CASE REPORT

Systemic Cat Scratch Disease

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Systemic cat scratch disease (CSD) is often associated with prolonged fever and microabscesses in the liver and/or spleen. We report a case of systemic CSD with hepatic, splenic and renal involvement in an aboriginal child in Taiwan. A previously healthy 9-year-old girl had an intermittent fever for about 17 days, and complained of abdominal pain, headache and weight loss. Abdominal computed tomography showed multiple tiny hypodense nodular lesions in the spleen and both kidneys. Laparotomy revealed multiple soft, whitish-tan lesions on the surface of the liver and spleen. Histopathologic examination of a biopsy specimen of the spleen showed necrotizing granulomatous inflammation with central necrosis surrounded by epithelioid cells and occasional Langhans' giant cells, strongly suggestive of *Bartonella henselae* infection. History revealed close contact with a cat. *B. henselae* DNA was detected by polymerase chain reaction in the tissue specimen, and the single antibody titer against *B. henselae* was greater than 1:2048. These results confirmed the diagnosis of visceral CSD caused by *B. henselae*. The patient's symptoms resolved after treatment with rifampin and tetracycline. This case illustrates the need for inclusion of systemic CSD in patients with fever of unknown origin and abdominal pain. [*J Formos Med Assoc* 2006;105(8):674–679]

Key Words: *Bartonella henselae,* cat scratch disease

Cat scratch disease (CSD) is a common cause of subacute regional, self-limited lymphadenitis in children, who usually have contact with a cat or kitten.[1] The most common etiologic agent of CSD is thought to be *Bartonella henselae*, a fastidious, slow-growing, Gram-negative bacillus.[2,3] Typical CSD usually presents with a papule at the site of the scratch and regional lymphadenopathy.[1–3] Systemic CSD is often associated with a prolonged fever and microabscesses in the liver and/or spleen.[4] There have been several reports of hepatosplenic granulomas caused by *B. henselae*.[5–10] We report a healthy 9-year-old girl with systemic CSD caused by *B. henselae*.

Case Report

A previously healthy 9-year-old aboriginal girl had a persistent fever of 38–39°C for about 17 days accompanied by left lower back pain, weight loss and headache. She visited a local hospital 6 days after the onset of her illness and was presumptively treated for acute bronchitis and urinary tract infection for 11 days. However, the fever persisted, and she was referred to our hospital for evaluation. The family had three dogs in the house and the neighbors had some domestic pigs and chickens. She had slept with a cat at night, which was kept outside during the day. She also frequently ate raw fish.

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Received: January 12, 2005
Revised: March 29, 2005
Accepted: October 4, 2005

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On admission, body temperature was 37.8°C, blood pressure was 98/75 mmHg, heart rate was 95/minute, and respiratory rate was 24/minute. Neither peripheral lymphadenopathy nor hepatosplenomegaly was detected. On physical examination, there were no specific dermatologic findings, including any eschar, scratch or bite wound by insects or animals. White blood cell count was 9260/mm^3, with 58% neutrophils and 32% lymphocytes. The erythrocyte sedimentation rate during the first hour was 104 mm. Urinalysis was negative and renal function was within normal limits. Antibody screening tests to cytomegalovirus, Epstein–Barr virus and *Mycoplasma pneumoniae* as well as Weil–Felix test, Widal test, rheumatic factor and anti-nuclear antibody were all negative. Bacterial and fungal cultures of the bone marrow and blood yielded no growth. A purified protein derivative skin test was negative. On admission, chest X-ray was normal. She had a daily spiking fever of 38–39°C in the afternoon or early morning without relative bradycardia. On day 5, she complained of left upper quadrant abdominal pain, headache, nausea and vomiting. Abdominal computed tomography (CT) showed multiple tiny, hypodense nodular lesions in the spleen and both kidneys without para-aortic lymph node enlargement (Figure 1A and B). Brain CT was normal. Cerebral spinal fluid studies and serum antibody titers to *Rickettsia typhi* and *Rickettsia burnetii* were negative. Follow-up abdominal echogram and abdominal CT 8 days later showed progression of the nodular lesions in the spleen and both kidneys (Figure 1C and D). On day 21, exploratory laparotomy with partial splenectomy revealed multiple soft, whitish-tan lesions on the surfaces of the liver and spleen (Figure 2A and B). Pathologic examination with hematoxylin and eosin stain of the

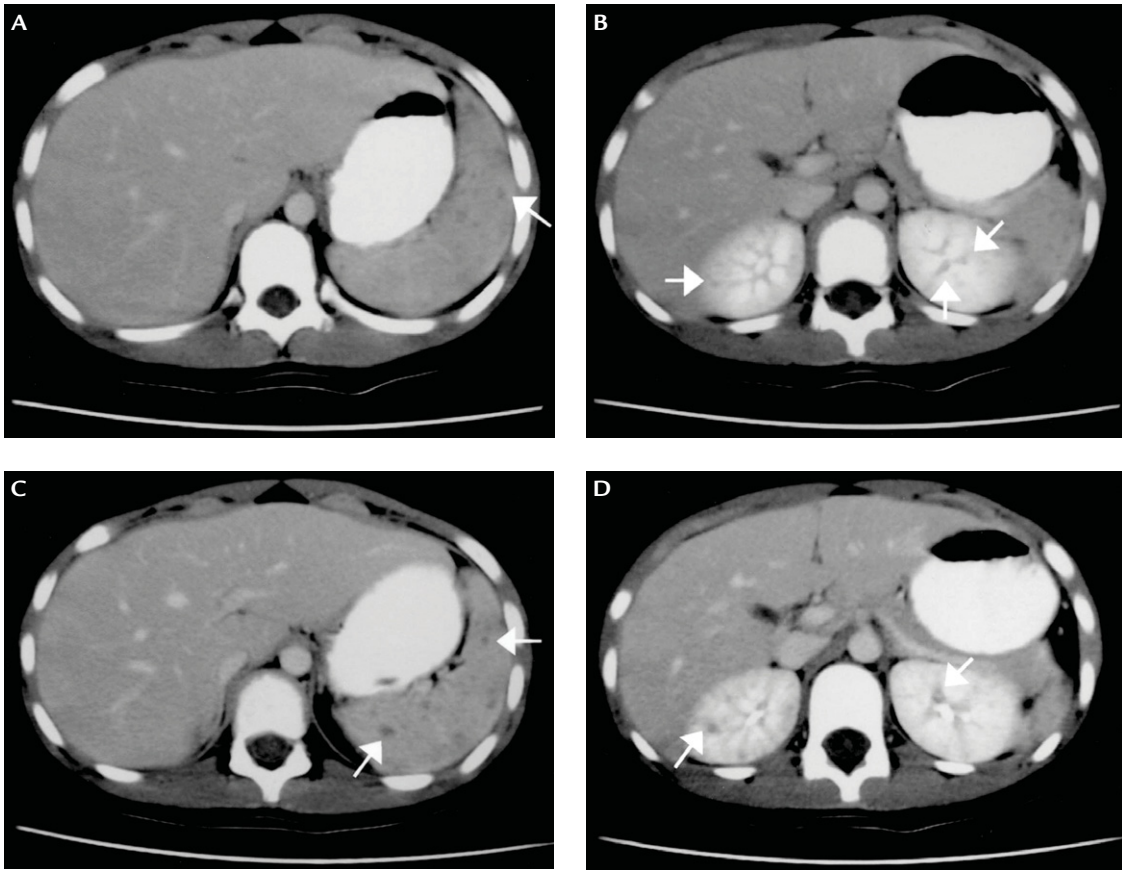

Figure 1. Contrast-enhanced abdominal computed tomography (CT) showing multiple small hypodense nodular lesions (arrows) within the: (A) spleen, and (B) both kidneys. Follow-up CT 8 days later showing the progression of hypodense nodular lesions (arrows) in the (C) spleen, and (D) kidneys.

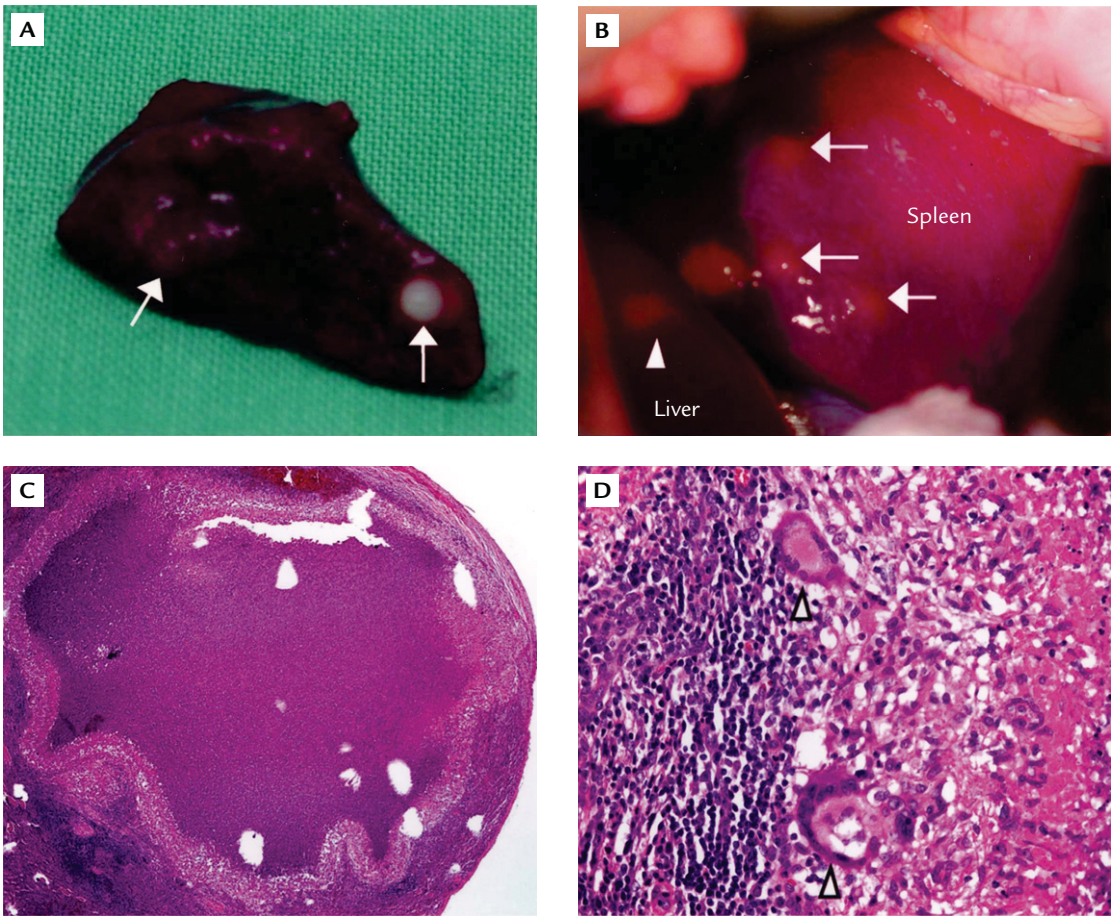

Figure 2. (A, B) Whitish-tan soft lesions on the surface of the liver (arrowhead) and spleen (arrows) at surgery. (C) Low-power view of the spleen biopsy showing necrotizing granulomatous inflammation with central necrosis (hematoxylin & eosin, 40×). (D) High-power view showing central necrosis surrounded by epithelioid cells and Langhans' giant cells (arrowheads) (hematoxylin & eosin, 200×).

splenic tissue showed necrotizing granulomatous inflammatory changes with central necrosis surrounded by epitheloid cells and a few occasional Langhans' giant cells (Figure 2C and D). Stains for fungus and acid-fast microorganisms were negative.

Serum antibody titer against *B. henselae* was greater than 1:2048 by indirect immunofluorescence antibody test (IFA). This technique employed a volume of 30 µL of suspension containing *B. henselae* (ATCC 49882)[11] infected cells coated on Teflon-printed slides (Electron Microscopy Science, USA). The serum was serially diluted from 1:32 to 1:512 by twofold dilutions using phosphate buffered saline (PBS, pH 7.4; with 10% skimmed milk). Thirty microliters of diluted serum was added to each well. Fluorescein-labeled goat antihuman immunoglobulin G (Kirkegaard & Perry Laboratories Inc., Gaithersburg, MD, USA) in 1:400 PBS dilution was then applied to each well. The intensity of the bacillus-specific fluorescence was scored subjectively from 1 to 4 by fluorescence microscope (magnification, ×400). A fluorescence score ≥2 at the dilution of 1:64 was considered to be positive.[11]

Polymerase chain reaction (PCR) was used to test the presence of *B. henselae* (Figure 3). Two sets of primers, PBH-1, PBH-2,[12] Hensela-A and Hensela-B, deduced from ridD, ribC and ribE genes of *B. henselae*, were used to identify *B. henselae*. PCR was carried out in a DNA thermal cycler (GeneAmp PCR System 9700; Perkin-Elmer, Foster City, CA, USA). The amplicon was sequenced using the ABI PRISM BigDye Terminator Cycle Sequencing Ready Reaction Kit and ABI Prism 377 Genetic Analyzer (PE Applied

Biosystems, Foster City, CA, USA). A positive result was indicated by the appearance of a single band of 345 bp in the specimens. Sequence analysis of this amplicon showed a totally identical genome to that of *B. henselae*.

The patient gradually improved during 4 weeks of tetracycline and rifampin treatment and was discharged on day 28 with continued prescription of these antibiotics. Follow-up abdominal CT scan showed resolution of the liver, spleen and kidney lesions 5 months later. Immune studies (including immunoglobins, C3, C4 and CH50 levels) performed 2 months later were within normal limits.

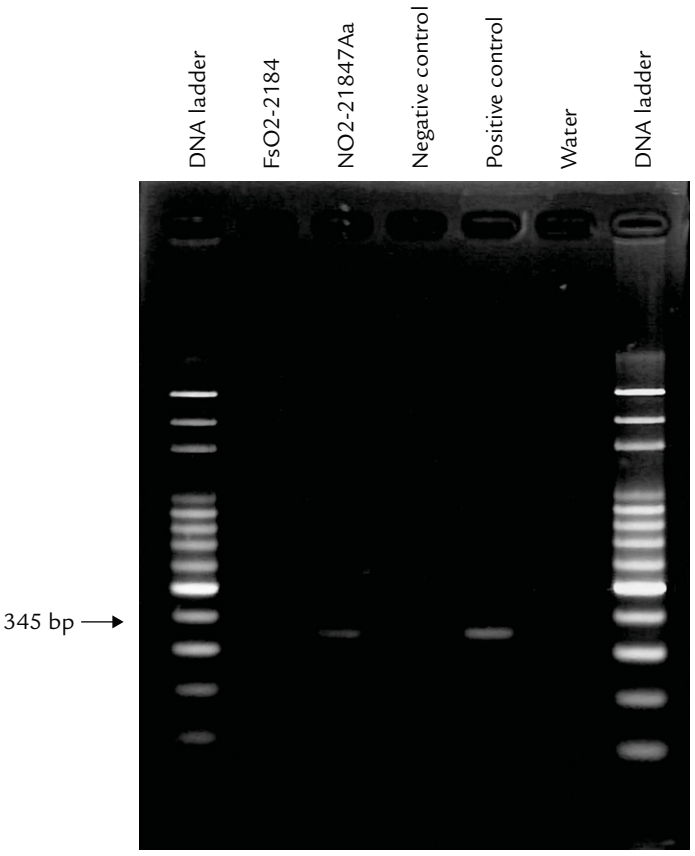

Figure 3. A 345-bp amplicon showing positive identification of *Bartonella henselae*.

Discussion

Systemic CSD is a clinical entity caused by *B. henselae,* which manifests with necrotizing granulomas in visceral organs. This microorganism was first identified as the cause of this disease in 1983, having eluded detection for 50 years. Initially, *Afipia felis* was thought to be the etiology; however, subsequent studies failed to confirm a correlation. During the 1990s, the fastidious Gram-negative bacillus *Rochalimaea henselae* was initially identified, but on the basis of genomic sequence analysis, it was subsequently reclassified in the genus *Bartonella*.[13]

CSD occurs at all ages, but most of the patients are aged under 10 years, with a median of 8.6 years. Lien et al[14] reported a male gender predominance (54–60%). The organisms apparently spread from the site of inoculation, usually a cat-inflicted injury.[6] The most common clinical presentation of typical CSD is lymphadenopathy, often involving the nodes that drain inoculation sites in the neck, axillary, epitrochlear or inguinal areas.

The most plausible mode of the spread of infection to the liver and spleen is hematogenous.[15] A patient with hepatic lesions was first described in 1985.[4] Systemic *B. henselae* infection has been reported in immunocompetent children who had prolonged fever and multiple granulomatous lesions in the liver and spleen.[4–10] Associated acute glomerulonephritis has also been reported.[16,17] In addition to liver and spleen lesions, our patient had renal microabscesses, a manifestation not previously reported in the English literature.

Prolonged fever associated with abdominal pain, weight loss, chills, headache and myalgia are the most common symptoms of systemic CSD.[10] Abdominal pain has been suggested to be an important symptom implicating visceral involvement.[8] Physical findings such as hepatomegaly, splenomegaly and lymphadenopathy were reported in CSD.[9,10] Peripheral lymphadenitis may be a diagnostic clue of CSD; however, only one-fourth of the patients in a series of 19 patients with hepatosplenic involvement had lymphadenitis.[10]

Abdominal ultrasound is helpful in the evaluation of systemic CSD. The findings of multiple-hypoechogenic lesions in the liver and/or spleen are suggestive of the diagnosis in the appropriate clinical setting.[9] Hepatic and splenic granulomas appear on CT scan as lesions with low attenuation

scattered throughout the liver and spleen.[18,19] Definitive diagnosis of systemic CSD, however, requires invasive investigation, including liver or spleen biopsy.[9,19] The diagnosis of *Bartonella* infection must be established by one or more means: histopathologic examination of biopsy specimens,[20] serologic evaluation,[11,21,22] microbiologic culture and/or use of PCR to detect DNA in tissue specimens.[22–24] Culture of the organism is not practical for clinical diagnosis and the traditional cat scratch skin test is no longer used and has been supplanted by sensitive serologic tests.[25] Different serologic tests (including IFA or EIA) vary in sensitivities and specificities because of the timing of the *B. henselae* IgG and IgM response and cross-reaction with antibodies to *B. quitana*.[14] Sander et al found IFA to be the most frequent and reliable serologic test.[26] PCR is a sensitive method for detecting *Bartonella* DNA which can even identify the species and genotypes by exploiting minor sequence differences. This permits differentiation between *B. henselae* and *B. quintana* and makes PCR the best method to confirm clinically, serologically or histologically suspected diagnosis of CSD.[27–29] Our patient had a positive antibody to *B. henselae* and a positive PCR result.

There is limited evidence of a beneficial effect of antibiotic treatment in disseminated *B. henselae* infection in the immunocompetent host.[3] A review of treatment outcome found that rifampicin, trimethoprim-sulfamethoxazole (TMP-SMZ) and ciprofloxacin appear to be effective.[30] Rifampicin has been reported to give a favorable clinical response in children with hepatosplenic CSD.[10] Another study found dramatic response to treatment with rifampicin and doxycycline.[19] Our patient's symptoms resolved after treatment with rifampicin and tetracycline, and the lesions on CT scan disappeared. Although we did not obtain actual tissue confirmation of *B. henselae* in the renal lesions, the fact that they disappeared at the same time as the hepatic and splenic lesions strongly suggests that they were manifestations of the systemic infection.

In conclusion, systemic CSD should be included in the differential diagnosis of children with fever of unknown origin, abdominal pain and elevated erythrocyte sedimentation rate. A key to the diagnosis is a history of contact with a cat or kitten. Imaging studies may suggest the diagnosis, and specific serology may confirm it, perhaps avoiding the need for biopsy.

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